1: Proc Natl Acad Sci U S A. 1996 Oct 1;93(20):10972-7. Related Articles, Links

Vaccination with syngeneic, lymphoma-derived immunoglobulin idiotype combined with granulocyte/macrophage colony-stimulating factor primes mice for a protective T-cell response.

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The idiotype of the Ig expressed by a B-cell malignancy (Id) can serve as a unique tumor-specific antigen and as a model for cancer vaccine development. In murine models of Id vaccination, formulation of syngeneic Id with carrier proteins or adjuvants induces an anti-idiotypic antibody response. However, inducing a potent cell-mediated response to this weak antigen instead would be highly desirable. In the 38C13 lymphoma model, we observed that low doses of free granulocyte/macrophage colony-stimulating factor (GM-CSF) 10,000 units i.p. or locally s.c. daily for 4 days significantly enhanced protective antitumor immunity induced by s.c. Id-keyhole limpet hemocyanin (KLH) immunization. This effect was critically dependent upon effector CD4+ and CD8+ T cells and was not associated with any increased anti-idiotypic antibody production. Lymphocytes from spleens and draining lymph nodes of mice primed with Id-KLH plus GM-CSF, but not with Id-KLH alone, demonstrated significant proliferation to Id in vitro without any biased production of interferon gamma or interleukin 4 protein or mRNA. As a further demonstration of potency, 50% of mice immunized with Id-KLH plus GM-CSF on the same day as challenge with a large s.c. tumor inoculum remained tumor-free at day 80, compared with 17% for Id-KLH alone, when immunization was combined with cyclophosphamide. Taken together, these results demonstrate that GM-CSF can significantly enhance the immunogenicity of a defined self-antigen and that this effect is mediated exclusively by activating the T-cell arm of the immune response.

PMID: 8855293 [PubMed - indexed for MEDLINE]

1: Int J Cancer. 1999 Oct 8;83(2):215-22. Related Articles, Links

Idiotypic protein-pulsed dendritic cell vaccination in multiple myeloma.

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Idiotypic protein (Id) produced by myeloma cells is clone-specific and may be a suitable tumor-specific antigen for immune targeting. Advances in dendritic cell (DC) technology suggest the opportunity for using this potent antigen presentation system to deliver myeloma Id to the autologous host to elicit anti-tumor immune responses. We have generated DCs from adherent PBMCs from 6 patients with IgG myeloma. These cells were pulsed with the autologous Id and a control vaccine, KLH, and re-infused i.v. back to the patients on 3 separate occasions. Immune responses to KLH and autologous Id were measured and clinical responses monitored. We found that all treatments were well tolerated without any side effects. All patients developed both B- and T-cell responses to KLH, suggesting the integrity of the host immune system to mount immune responses to an antigen delivered using our vaccination strategy. Id-specific responses were also observed. PBMC proliferative responses to Id were observed in 5 of the 6 patients following treatment. In 2 patients, the responses were associated with the production of IFN-gamma. There were also increases in cytotoxic T-cell precursor frequencies for Id-pulsed autologous targets in 3 patients. B-cell responses characterized by the production of anti-Id IgM occurred in 3 and anti-Id IgG in 4 of the 5 evaluated patients. In 1 patient, a modest (25%) but consistent drop in the serum Id level was observed. Id-pulsed DC vaccination can therefore elicit potentially useful anti-myeloma immune responses in patients with multiple myeloma.

Publication Types:
- Clinical Trial

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1: Nat Med. 1998 Mar;4(3):328-32. Related Articles, Links

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- Nat Med. 1998 Mar;4(3):269-70.

Vaccination of melanoma patients with peptide- or tumor lysate-pulsed dendritic cells.

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Melanoma is the main cause of death in patients with skin cancer. Cytotoxic T lymphocytes (CTLs) attack melanoma cells in an HLA-restricted and tumor antigen-specific manner. Several melanoma-associated tumor antigens have been identified. These antigens are suitable candidates for a vaccination therapy of melanoma. Dendritic cells (DCs) are antigen-presenting cells (APCs) specialized for the induction of a primary T-cell response. Mouse studies have demonstrated the potent capacity of DCs to induce antitumor immunity. In the present clinical pilot study, DCs were generated in the presence of granulocyte/macrophage-colony stimulating factor (GM-CSF) and interleukin 4 (IL-4) and were pulsed with tumor lysate or a cocktail of peptides known to be recognized by CTLs, depending on the patient's HLA haplotype. Keyhole limpet hemocyanin (KLH) was added as a CD4 helper antigen and immunological tracer molecule. Sixteen patients with advanced melanoma were immunized on an outpatient basis. Vaccination was well tolerated. No physical sign of autoimmunity was detected in any of the patients. DC vaccination induced delayed-type hypersensitivity (DTH) reactivity toward KLH in all patients, as well as a positive DTH reaction to peptide-pulsed DCs in 11 patients. Recruitment of peptide-specific CTLs to the DTH challenge site was also demonstrated. Therefore, antigen-specific immunity was induced during DC vaccination. Objective responses were evident in 5 out of 16 evaluated patients (two complete responses, three partial responses) with regression of metastases in various organs (skin, soft tissue, lung, pancreas) and one additional minor response. These data indicate that vaccination with autologous DCs generated from peripheral blood is a safe and promising approach in the treatment of metastatic melanoma. Further studies are necessary to demonstrate clinical effectiveness and impact on the survival of melanoma patients.

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